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APPLICATION NUMBER:

200327

OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	October 29, 2010
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	NDA# 200327
Applicant Name	Cerexa
Date of Submission	December 30, 2009
PDUFA Goal Date	October 30, 2010
Proprietary Name (proposed) / **Established (USAN) Name**	Teflaro ceftaroline fosamil
Dosage Forms / Strength	Injection for intravenous use single use vials of 600mg or 400mg of Teflaro powder in 20ml vials for reconstitution
Proposed Indication(s)	Treatment of the following infections caused by designated susceptible bacteria • acute bacterial skin and skin structure infections (ABSSSI) • community-acquired bacterial pneumonia (CABP)
Action:	Approval

This memo focuses on selected topics from the review of the NDA for ceftaroline. For a more detailed review, the reader is referred to the discipline specific reviews, the Cross-Discipline Team Leader Review and the Deputy Division Director's Review. I concur with the assessments of the review team, the CDTL, and the Deputy Division Director regarding ceftaroline that substantial evidence of safety and effectiveness has been presented for ceftaroline for the indications of ABSSSI and CABP.

Teflaro (ceftaroline fosamil) is a cephalosporin antibacterial agent. Ceftaroline fosamil is a water soluble pro-drug that is rapidly converted to its active form, ceftaroline, by in vivo phosphatases. Ceftaroline is active against certain gram-positive and gram-negative bacteria. It acts through binding to penicillin binding proteins (PBP) and retains affinity for PBP2a; in *in vitro* testing, it has activity against methicillin-resistant isolates of *Staphylococcus aureus*.

Ceftaroline is supplied as a sterile powder for reconstitution and intravenous administration. The Chemistry reviewer finds that adequate information has been provided to assure the identity, strength, purity, and quality of the drug product and approval is recommended. The Product Quality Microbiology Reviewer recommends approval. Manufacturing facilities inspections are also found to be acceptable.

The Pharmacology/Toxicology reviewer recommends approval for ceftaroline. Ceftaroline is labeled as Pregnancy Category B. The Clinical Pharmacology reviewer finds that the information provided on the clinical pharmacology of ceftaroline is acceptable. The usual

adult dose for ceftaroline is 600 mg IV every 12h. The product labeling provides instructions for dosage adjustment in patients with a creatinine clearance of 50 mL/min or less. Ceftaroline does not appear to be significantly metabolized by the CYP450 metabolic pathway. Ceftaroline and its metabolites are predominantly eliminated via renal excretion. No dosage adjustment is recommended based upon age or gender. Based upon data from in vitro studies, ceftaroline is not an inhibitor or an inducer of major CYP450 enzymes; therefore drug interactions with CYP450 substrates are not likely. Ceftaroline was evaluated in a thorough QT study and was found not to significantly prolong the QT interval.

The Clinical Microbiology Reviewer recommends approval for the application. The reviewers have evaluated the available scientific information to arrive at the susceptibility test interpretive criteria in the product labeling. In the clinical trials for CABP, the comparator drug was ceftriaxone; therefore, patients with methicillin-resistant *S. aureus* (MRSA) were excluded from the CABP clinical trials.

The applicant performed 2 adequate and well-controlled trials in ABSSSI. The trials were designed with a primary endpoint of clinical response at 8-15 days after a 5-14 day course of therapy; this is an endpoint for which we have not been able to justify a non-inferiority margin. The Agency analyses focused on a responder endpoint of cessation of spread of lesion with the absence of fever at 48-72 hours. A justification for this margin is cited in the Statistical review for ABSSSI and described in more detail in an appendix to the recently published draft guidance document on ABSSSI. The analyses using this endpoint demonstrate efficacy for ceftaroline in ABSSSI. Additional analyses were also performed which did not include the fever component in the responder endpoint; these analyses also support the efficacy of ceftaroline in ABSSSI.

Two adequate and well-controlled trials were performed in CABP. Similar to ABSSSI, the originally chosen endpoint of investigator-assessment at 8-15 days after a 5-7 day course of therapy is an endpoint for which we have not been able to justify a non-inferiority margin. The Agency analyses utilized a responder analysis based upon improvement in signs and symptoms of disease by Day 4 in the microbiological intent-to-treat population. A justification for this margin is cited in the Statistical review for CABP and was also discussed at the December 9, 2009 Anti-Infective Drugs Advisory Committee meeting. The results from the analyses from the two CABP studies utilizing the responder analysis by Day 4 support the efficacy of ceftaroline for treatment of CABP.

The safety database for ceftaroline is derived from over 1700 subjects who received ceftaroline in clinical and pharmacokinetic studies. Of these subjects, over 1400 received the dose of 600 mg IV for 5-14 days. The rates of adverse effects were similar across treatment groups. Rates of serious adverse events and deaths were also similar across treatment groups. Examination of these events did not find an association between ceftaroline and an increased risk of deaths or SAEs. In the ceftaroline treated patients, a higher rate of direct Coombs' test seroconversion was noted in the 4 pooled phase 3 trials (10.8% ceftaroline vs. 4.4% comparator drugs). Further examination did not reveal an increased incidence of anemia or cases of hemolytic anemia in ceftaroline treated patients. The product labeling for ceftaroline

describes the higher rate of direct Coombs' test positivity for ceftaroline treated patients in the Warnings and Precautions section.

Ceftaroline was presented to the Anti-Infective Drugs Advisory Committee on September 7, 2010. On the question of whether safety and efficacy has been demonstrated for ceftaroline for CABP, the Committee voted Yes 21; No 0; abstain 0. On the question of whether safety and efficacy had been demonstrated for ABSSSI, the Committee voted Yes 18; No 0; abstain 0. Additional comments from the Committee included that they found the FDA analyses very helpful. They also noted that information should be included in labeling regarding positive direct Coombs' tests and that the labeling should note that ceftaroline is indicated for MRSA in ABSSSI and not for CABP.

The Division of Scientific Investigations performed audits of 8 clinical trial sites. Seven of the inspections were classified as NAI and one was classified as VAI. The findings from the site classified as VAI were not findings that raised concerns regarding the integrity of the data. Inspection of the applicant, Cerexa, did not reveal GCP violations. There was a clinical investigation site in India where the applicant identified problems. The applicant has followed-up appropriately on these findings. The data from 9 patients from this site and 2 other sites monitored by the same CRO have been excluded from the FDA analyses.

The action letter includes PMRs for required pediatric studies and for a study to monitor for rates of resistance to ceftaroline annually for a five year time period along with a postmarketing commitment to perform a CABP study in patients at high risk for MRSA infection.

Summary
I concur with the recommendations from the review team, the CDTL and the Deputy Division Director that substantial evidence of safety and efficacy has been provided for ceftaroline for the indications of ABSSSI and CABP. The analyses performed by the Agency evaluating responder endpoints at earlier timepoints in CABP and ABSSSI provides the essential analyses for assessing the efficacy of ceftaroline. The conclusion that safety and efficacy has been shown for ABSSSI and CABP, and the importance of the Agency analyses is also supported by the discussion of the application for ceftaroline at the September 7, 2010 Anti-Infective Drugs Advisory Committee meeting. The product labeling adequately describes the conditions of use and provides information on the risks and benefits of ceftaroline.

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/s/

EDWARD M COX
10/29/2010